

**PATENT**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of:  
G. Patrick Meier et al.

Serial No.: 10/575,188

Filed: April 7, 2006

For: SITE AND RATE SELECTIVE  
PRODRUG FORMULATIONS OF D609  
WITH ANTIOXIDANT AND  
ANTICANCER ACTIVITY

Group Art Unit: 1626

Examiner: Unknown

Atty. Dkt. No.: MESC:009US

Confirmation No.: 7144

**CERTIFICATE OF ELECTRONIC TRANSMISSION**  
37 C.F.R. § 1.8

I hereby certify that this correspondence is being  
electronically filed with the United States Patent and  
Trademark Office via EFS-Web on the date below:

February 13, 2007

Date

  
Michael R. Krawczenski

**INFORMATION DISCLOSURE STATEMENT**

**MS AMENDMENT**

Commissioner for Patents

P.O. Box 1450

Alexandria, Virginia 22313-1450

Sir:

In compliance with the duty of disclosure under 37 C.F.R. § 1.56, it is respectfully requested that this Information Disclosure Statement be entered and the documents listed on attached Form PTO-1449 be considered by the Examiner and made of record. Copies of the listed documents required by 37 C.F.R. § 1.98(a)(2) are enclosed for the convenience of the Examiner.

In accordance with 37 C.F.R. § 1.97(g), (h), this Information Disclosure Statement is not to be construed as a representation that a search has been made, and is not to be construed to be an admission that the information cited is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

The present Information Disclosure Statement is being filed prior to the receipt of a first Official Action reflecting an examination on the merits, and hence is believed to be timely filed in accordance with 37 C.F.R. § 1.97(b). No fees are believed to be due in connection with the filing of this Information Disclosure Statement, however, should any fees under 37 C.F.R. § 1.16 to 1.21 be deemed necessary for any reason relating to these materials, the Commissioner is authorized to deduct the appropriate fees from Fulbright & Jaworski Deposit Account No.: 50-1212/MESC:009US.

Applicants respectfully request that the listed documents be made of record in the present case.

Respectfully submitted,



Michael R. Krawcsenek  
Reg. No. 51,898  
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.  
600 Congress Avenue, Suite 2400  
Austin, Texas 78701  
(512) 474-5201

Date: February 13, 2007

Form PTO-1449 (modified)		Atty. Docket No. MESC:009US	Serial No. 10/575,188
List of Patents and Publications for Applicant's  INFORMATION DISCLOSURE STATEMENT  (Use several sheets if necessary)		Applicant: G. Patrick Meier <i>et al.</i>	
		Filing Date: April 7, 2006	Group: 1626
U.S. Patent Documents <i>See Page 1</i>	Foreign Patent Documents <i>See Page 1</i>	Other Art <i>See Page 1-4</i>	

### U.S. Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Name	Class	Sub Class	Filing Date of App.

### Foreign Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Country	Language

### Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C1	Amtmann and Sauer, "Selective killing of tumor cells by xanthates," <i>Cancer Lett.</i> , 35:237-244, 1987.
	C2	Amtmann and Sauer, "Tumor necrosis factor induces necrosis of human carcinoma xenografts in the presence of tricyclodecan-9-yl-xanthogenate and lauric acid," <i>Int. J. Cancer</i> , 45:1113-1118, 1990.
	C3	Amtmann, "The antiviral, antitumoural xanthate D609 is a competitive inhibitor of phosphatidylcholine-specific phospholipase C," <i>Drugs Exp. Clin. Res.</i> , 22:287-294, 1996.
	C4	Bai <i>et al.</i> , "Prodrug Modification Increases Potassium Tricyclo[5.2.1.0]-decan-8-yl Dithiocarbonate (D609) Chemical Stability and Cytotoxicity Against U937 Leukemia Cells," <i>J. of Pharmaceutical and Experimental Therapeutics</i> , 309:1051-1059, 2004.
	C5	Bettaieb <i>et al.</i> , "Daunorubicin- and mitoxantrone-triggered phosphatidylcholine hydrolysis: implication in drug-induced ceramide generation and apoptosis," <i>Mol. Pharmacol.</i> , 55:118-125, 1999.
	C6	Capizzi, "The preclinical basis for broad-spectrum selective cytoprotection of normal tissues from cytotoxic therapies by amifostine," <i>Semin. Oncol.</i> , 26:3-21, 1999.
	C7	Chevon <i>et al.</i> , "Evaluation of plasma low molecular weight antioxidant capacity by cyclic voltammetry," <i>Free Radic. Biol. Med.</i> , 22:411-421, 1997.

25714478.1

EXAMINER:

DATE CONSIDERED:

EXAMINER: INITIAL IF REFERENCE CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP609, DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED. INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT.

Form PTO-1449 (modified)		Atty. Docket No. MESC:009US	Serial No. 10/575,188
List of Patents and Publications for Applicant's		Applicant: G. Patrick Meier <i>et al.</i>	
INFORMATION DISCLOSURE STATEMENT		Filing Date: April 7, 2006	Group: 1626
(Use several sheets if necessary)			
U.S. Patent Documents <i>See Page 1</i>	Foreign Patent Documents <i>See Page 1</i>	Other Art <i>See Page 1-4</i>	

### Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C8	Culy and Spencer, "Amifostine: An Update on its Clinical Status as a Cytoprotectant in Patients with Cancer Receiving Chemotherapy or Radiotherapy and its Potential Therapeutic Application in Myelodysplastic Syndrome," <i>Drugs</i> , 61:641-684, 2001.
	C9	Druker and Lydon, "Lessons learned from the development of an abl tyrosine kinase inhibitor for chronic myelogenous leukemia," <i>J. Clin. Invest.</i> , 105:3-7, 2000.
	C10	Furstenberger <i>et al.</i> , "Tumor prevention by a xanthate compound in experimental mouse-skin tumorigenesis," <i>Int. J. Cancer</i> , 43:508-512, 1989.
	C11	Gazdar and Minna, "Targeted therapies for killing tumor cells," <i>Proc. Natl. Acad. Sci. USA</i> , 98:10028-10030, 2001.
	C12	Gibbs, "Mechanism-Based Target Identification and Drug Discovery in Cancer Research," <i>Science</i> , 287:1969-1973, 2000.
	C13	Giron-Calle <i>et al.</i> , "Priming of alveolar macrophage respiratory burst by H(2)O(2) is prevented by phosphatidylcholine-specific phospholipase C inhibitor Triclyclodecan-9-yl-xanthate (D609)," <i>J. Pharmacol. Exp. Ther.</i> , 301:87-94, 2002.
	C14	Greenberger <i>et al.</i> , "Modulation of redox signal transduction pathways in the treatment of cancer," <i>Antioxid. Redox. Signal</i> , 3:347-359, 2001.
	C15	Hospers <i>et al.</i> , "The sulfhydryl containing compounds WR-2721 and glutathione as radio- and chemoprotective agents. A review, indications for use and prospects," <i>Br. J. Cancer</i> , 80:629-638, 1999.
	C16	Krise <i>et al.</i> , "A novel prodrug approach for tertiary amines. 2. Physicochemical and in vitro enzymatic evaluation of selected N-phosphonoxyethyl prodrugs," <i>J. Pharm. Sci.</i> , 88:922-927, 1999.
	C17	Krise <i>et al.</i> , "A novel prodrug approach for tertiary amines. 3. In vivo evaluation of two N-phosphonoxyethyl prodrugs in rats and dogs," <i>J. Pharm. Sci.</i> , 88:928-932, 1999.
	C18	Luberto and Hannun, "Sphingomyelin synthase, a potential regulator of intracellular levels of ceramide and diacylglycerol during SV40 transformation. Does sphingomyelin synthase account for the putative phosphatidylcholine-specific phospholipase C?" <i>J. Biol. Chem.</i> , 273:14550-14559, 1998.

25714478.1

EXAMINER:

DATE CONSIDERED:

EXAMINER: INITIAL IF REFERENCE CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP609; DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED. INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT.

Form PTO-1449 (modified)		Atty. Docket No. MESC:009US	Serial No. 10/575,188
List of Patents and Publications for Applicant's		Applicant: G. Patrick Meier <i>et al.</i>	
INFORMATION DISCLOSURE STATEMENT		Filing Date: April 7, 2006	Group: 1626
(Use several sheets if necessary)			
U.S. Patent Documents <i>See Page 1</i>	Foreign Patent Documents <i>See Page 1</i>	Other Art <i>See Page 1-4</i>	

### Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C19	Luberto <i>et al.</i> , "Differential effects of sphingomyelin hydrolysis and resynthesis on the activation of NF-kappa B in normal and SV40-transformed human fibroblasts," <i>J. Biol. Chem.</i> , 275:14760-14766, 2000.
	C20	Machleidt <i>et al.</i> , "Function of the p55 tumor necrosis factor receptor "death domain" mediated by phosphatidylcholine-specific phospholipase C," <i>J. Exp. Med.</i> , 184:725-733, 1996.
	C21	Meng <i>et al.</i> , "Sphingomyelin synthase as a potential target for D609-induced apoptosis in U937 human monocytic leukemia cells," <i>Exp. Cell Res.</i> , 292:385-392, 2004.
	C22	Nudelmann <i>et al.</i> , "Prodrugs of butyric acid. Novel derivatives possessing increased aqueous solubility and potential for treating cancer and blood diseases," <i>Eur. J. Med. Chem.</i> , 36:63-74, 2001.
	C23	Paris <i>et al.</i> , "Endothelial Apoptosis as the Primary Lesion Initiating Intestinal Radiation Damage in Mice," <i>Science</i> , 293:293-297, 2001.
	C24	PCT International Search Report, May 13, 2005.
	C25	Perry and Ridgway, "The role of de novo ceramide synthesis in the mechanism of action of the tricyclic xanthate D609," <i>J. Lipid Res.</i> , 45:164-173, 2004.
	C26	Poggi <i>et al.</i> , "Sensitizers and protectors of radiation and chemotherapy," <i>Curr. Probl. Cancer</i> , 25:334-411, 2001.
	C27	Porn-Ares <i>et al.</i> , "Induction of apoptosis and potentiation of TNF- and Fas-mediated apoptosis in U937 cells by the xanthogenate compound D609," <i>Exp. Cell Res.</i> , 235:48-54, 1997.
	C28	Rao, <i>Xanthates and Related Compounds</i> , Marcel Dekker, Inc., NY, 1971.
	C29	Riboni <i>et al.</i> , "Basic fibroblast growth factor-induced proliferation of primary astrocytes. evidence for the involvement of sphingomyelin biosynthesis," <i>J. Biol. Chem.</i> , 276:12797-12804, 2001.
	C30	Santana <i>et al.</i> , "Acid sphingomyelinase-deficient human lymphoblasts and mice are defective in radiation-induced apoptosis," <i>Cell</i> , 86:189-199, 1996.
	C31	Sauer <i>et al.</i> , "Systemic treatment of a human epidermoid non-small cell lung carcinoma xenograft with a xanthate compound causes extensive intratumoral necrosis," <i>Cancer Lett.</i> , 53:97-102, 1990.

25714478.1

EXAMINER:

DATE CONSIDERED:

EXAMINER. INITIAL IF REFERENCE CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP609. DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED. INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT.

Form PTO-1449 (modified)		Atty. Docket No. MESC:009US	Serial No. 10/575,188
List of Patents and Publications for Applicant's		Applicant: G. Patrik Meier <i>et al.</i>	
INFORMATION DISCLOSURE STATEMENT		Filing Date: April 7, 2006	Group: 1626
(Use several sheets if necessary)			
U.S. Patent Documents <i>See Page 1</i>	Foreign Patent Documents <i>See Page 1</i>	Other Art <i>See Page 1-4</i>	

### Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C32	Schick <i>et al.</i> , "Antitumoral activity of a xanthate compound. I. Cytotoxicity studies with neoplastic cell lines in vitro" <i>Cancer Lett.</i> , 46:143-147, 1989.
	C33	Schick <i>et al.</i> , "Antitumoral activity of a xanthate compound. II. Therapeutic studies in murine leukemia and tumor models in vivo," <i>Cancer Lett.</i> , 46:149-152, 1989.
	C34	Schutze <i>et al.</i> , "TNF activates NF-kappa B by phosphatidylcholine-specific phospholipase C-induced "acidic" sphingomyelin breakdown," <i>Cell</i> , 71:765-776, 1992.
	C35	Schutze <i>et al.</i> , "Tumor necrosis factor induces rapid production of 1'2'diacylglycerol by a phosphatidylcholine-specific phospholipase C," <i>J. Exp. Med.</i> , 174:975-988, 1991.
	C36	Smith and Clark, In: <i>Drug latention and prodrugs</i> , Delgado and Remers (Eds.), Lippincott-Raven Publishers, Philadelphia, 123-138, 1998.
	C37	Spencer and Goa, "Amifostine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential as a radioprotector and cytotoxic chemoprotector," <i>Drugs</i> , 50:1001-1031, 1995.
	C38	Zhou <i>et al.</i> , "D609 inhibits ionizing radiation-induced oxidative damage by acting as a potent antioxidant," <i>J. Pharmacol. Exp. Ther.</i> , 298:103-109, 2001.
	C39	Zhou <i>et al.</i> , "Effects of NF-kappaB1 (p50) targeted gene disruption on ionizing radiation-induced NF-kappaB activation and TNFalpha, IL-1alpha, IL-1beta and IL-6 mRNA expression in vivo," <i>Int. J. Radiat. Biol.</i> , 77:763-772, 2001.

25714478.1

EXAMINER:

DATE CONSIDERED:

EXAMINER: INITIAL IF REFERENCE CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP609; DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED. INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT.